

WHAT IS CLAIMED IS:

1. The use of the FPRL1 receptor as a tool to identify compounds effective in treating inflammation and associated pain.
2. The use of the FPRL1 receptor as a screening tool to identify compounds effective in treating inflammation and associated pain.
3. The use of compounds specifically active at the FPRL1 receptor as therapeutics for treating inflammation and associated pain.
4. The prophylactic use of compounds specifically active at the FPRL1 receptor as therapeutics for blocking inflammation and associated pain.
5. A method of screening for a compound able to affect one or more activities of a FPRL1 receptor comprising the steps of,
 - a) contacting a recombinant cell with a test compound, wherein said recombinant cell comprises a recombinant nucleic acid expressing said FPRL1 receptor, provided that said cell does not have functional FPRL1 receptor expression from endogenous nucleic acid, and
 - b) determining the ability of said test compound to affect one or more activities of said FPRL1 receptor, and comparing said ability with the ability of said test compound to affect said one or more FPRL1 receptor activities in a cell not comprising said recombinant nucleic acid;
wherein said recombinant nucleic acid comprises a FPRL1 receptor nucleic acid selected from the group consisting of:
 - i) nucleic acid of SEQ ID NO 1,
 - ii) nucleic acid encoding the amino acid SEQ ID NO 2,
 - iii) a derivative of either nucleic acid molecule in i) or ii), wherein said derivative encodes a receptor having one or more activities of said FPRL1 receptor and comprises at least 20 contiguous nucleotides which can hybridize under stringent hybridization conditions to the complement of the nucleic acid of SEQ ID NO:1.
6. The method of Claim 5, wherein said FPRL1 receptor nucleic acid encodes the amino acid sequence of a SEQ ID NO 2 derivative comprising at least 20 contiguous nucleotides which can hybridize under stringent hybridizations conditions to a complement of at least 20 contiguous nucleotides encoding the amino acid sequence of SEQ ID NO 2.

7. A method for treating acute and chronic inflammation of any type comprising contacting an organism with an effective amount of at least one compound of Formula I, II, or III, wherein the compound activates a FPRL1 receptor subtype.

8. The method of Claim 7 wherein the inflammation is associated with diabetes, viral infection, irritable bowel syndrome, amputation, cancer, bacterial infection, physical injury, including physical trauma and radiation exposure, vasoconstriction as a result of asthma, anaphylactic reactions, allergic reactions, shock, diabetes, rheumatoid arthritis, gout, psoriasis, allergic rhinitis, adult respiratory distress syndrome, Crohn's disease, endotoxin shock, traumatic shock, hemorrhagic shock, bowel ischemic shock, renal glomerular disease, benign prostatic hypertrophy, myocardial ischemia, myocardial infarction, circulatory shock, brain injury including ischaemic stroke and hemorrhagic stroke, systemic lupus erythematosus, chronic renal disease, cardiovascular disease, and hypertension or chemical injury.

9. A method of identifying a compound which is an agonist of the FPRL1 receptor, the method comprising:

contacting a FPRL1 receptor with at least one test compound of Formula I, II, or III;
and

determining any increase in activity level of said FPRL1 receptor so as to identify a test compound which is an agonist of the FPRL1 receptor.

10. A method of identifying a compound which is an agonist of a FPRL1 receptor, the method comprising:

culturing cells that express said FPRL1 receptor;
incubating the cells or a component extracted from the cells with at least one test compound of Formula I, II, or III; and
determining any increase in activity of said FPRL1 receptor so as to identify a test compound which is an agonist of a FPRL1 receptor.

11. The method of Claim 10, wherein the cultured cells overexpress said FPRL1 receptor.

12. The method of Claim 9 or 10, wherein the identified agonist is selective for the FPRL1 receptor.

13. A method for treating inflammation comprising

contacting an individual suffering from inflammation with an effective amount of at least one compound of Formula I, II, or III,

whereby one or more symptoms of the inflammation is reduced.

14. The method of Claim 13 further comprising the step of identifying an individual in need of inflammatory treatment prior to the contacting step.

15. The method of Claim 13, wherein said compound of Formula I, II, or III selectively activates the FPRL1 receptor subtype.

16. The method of Claim 13, wherein the inflammatory response results from the activation of leukocytes, which activation comprises leukocyte migration and generation of reactive oxygen species to evoke vascular leakage or edema.

17. The method of Claim 13, wherein the inflammatory response is associated with rheumatoid arthritis, Alzheimer's disease or asthma.

18. The method of Claim 13, wherein the inflammatory response results from physical injury, including physical trauma and radiation exposure.

19. A method for treating or preventing inflammation or an inflammatory response in the subject, comprising: administering to a subject an effective anti-inflammatory amount of a compound of Formula I, II, or III.

20. A method of inducing vasodilation to treat or prevent a vasoconstrictive response or condition, comprising: administering to a subject an effective vasodilatory amount of a compound of Formula I, II, or III.

21. A method of Claim 20, wherein the vasoconstrictive response or condition is selected from the group consisting of a renal hemodynamic disease, including glomerular disease, and a cardiovascular disease, including hypertension, myocardial infarction, and myocardial ischemia.

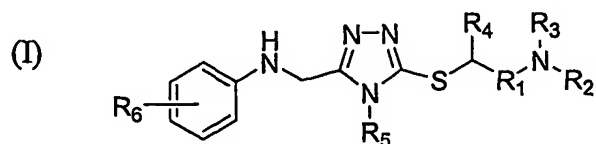
22. A method for antagonizing a vasoconstrictive response to a sulfidopeptide leukotriene in a subject, comprising: administering to the subject a composition of Formula I, II, or III.

23. The method of Claim 22, wherein the vasoconstrictive response to said leukotriene is associated with a medical disorder selected from the group consisting of: asthma, anaphylactic reactions, allergic reactions, shock, inflammation, rheumatoid arthritis, gout, psoriasis, allergic rhinitis, adult respiratory distress syndrome, Crohn's disease, endotoxin shock, traumatic shock, hemorrhagic shock, bowel ischemic shock, renal glomerular disease, benign prostatic hypertrophy, inflammatory bowel disease, myocardial ischemia, myocardial infarction, circulatory shock, brain injury, systemic lupus erythematosus, chronic renal disease, cardiovascular disease, and hypertension.

24. The method of Claim 22, wherein the vasoconstrictive response is a renal vasoconstrictive response, including mild vasoconstriction, such as chronic renal disease, and chronic severe vasoconstriction, such as glomerular kidney disease.

25. A method for stimulating cell proliferation in a subject to treat or prevent myeloid suppressive disorders comprising: administering to the subject an effective amount of the compound of Formula I, II, or III.

26. A compound of Formula I



or a pharmaceutically acceptable salt, ester, amide, or prodrug thereof,
wherein

R_1 is selected from the group consisting of C_1 - C_{10} straight chained or branched alkylene, oxygen, sulfur, NQ, CHCN, $C=O$, $C=S$, $C=NQ$, $S=O$, $S(=O)_2$, $C=NOQ$,

wherein Q is independently selected from the group consisting of hydrogen, C_1 - C_{10} straight chained or branched alkyl optionally substituted with an aryl or heteroaryl, C_2 - C_{10} straight chained or branched alkenyl optionally substituted with an aryl or heteroaryl, C_2 - C_{10} straight chained or branched alkynyl optionally substituted with an aryl or heteroaryl, C_3 - C_{10} cycloalkyl, and C_5 - C_{10} cycloalkenyl;

each of R_2 , R_3 , R_4 , and R_5 is independently selected from the group consisting of hydrogen, C_1 - C_{10} straight chained or branched alkyl, C_2 - C_{10} straight chained or branched alkenyl, C_2 - C_{10} straight chained or branched alkynyl, C_3 - C_{10} cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, hydroxy, halogenated ether, nitro, amino, halogen, perhaloalkyl, $-OR_7$, $-N(R_7)_2$, $-CN$, $-C(=Z)R_7$, $-C(=Z)OR_7$, $-C(=Z)N(R_7)_2$, $-N(R_7)-C(=Z)R_7$, $-N(R_7)-C(=Z)N(R_7)_2$, $-OC(=Z)R_7$, and $-SR_7$,

wherein Z is oxygen or sulfur; and wherein each R_7 is independently selected from the group consisting of hydrogen, C_1 - C_{10} straight chained or branched alkyl

optionally substituted with an aryl or heteroaryl, C₂-C₁₀ straight chained or branched alkenyl optionally substituted with an aryl or heteroaryl, C₂-C₁₀ straight chained or branched alkynyl optionally substituted with an aryl or heteroaryl, C₃-C₁₀ cycloalkyl, and C₅-C₁₀ cycloalkenyl; or

R₃ and R₄ and the nitrogen to which they are attached form a fused heteroaryl, or heterocyclic ring.

R₆ may be present 0-5 times and is independently selected from the group consisting of hydrogen, C₁-C₄ straight chained or branched alkyl, cycloalkyl, aryl or heteroaryl optionally substituted, hydroxy, nitro, amino, halogen, sulphonate, perhaloalkyl, -OR₇, -N(R₈)₂, -CN, -C(=Z)R₈, -C(=Z)OR₈, -C(=Z)N(R₈)₂, -N(R₈)-C(=Z)R₈, -N(R₈)-C(=Z)N(R₈)₂, -OC(=Z)R₈, and -SR₈,

wherein Z is oxygen or sulfur; and wherein each R₈ is independently selected from the group consisting of hydrogen, C₁-C₁₀ straight chained or branched alkyl optionally substituted with an aryl or heteroaryl, C₂-C₁₀ straight chained or branched alkenyl optionally substituted with an aryl or heteroaryl, C₂-C₁₀ straight chained or branched alkynyl optionally substituted with an aryl or heteroaryl, C₃-C₁₀ cycloalkyl, and C₅-C₁₀ cycloalkenyl; or

"R₆" form a fused aryl or heteroaryl ring

27. The compound of Claim 26, wherein R₁ is hydrogen or C₁-C₁₀ straight chained alkyl.

28. The compound of Claim 26, wherein R₁ is C₁-C₅ straight chained alkylene.

29. The compound of Claim 28, wherein R₁ is selected from the group consisting of methylene, ethylene, n-propylene, isopropylene, n-butylene, sec-butylene, tert-butylene, n-pentylene, and isopentylene.

30. The compound of Claim 26, wherein R₂ is selected from the group consisting of hydrogen, hydroxy, nitro, amino, aryl, heteroaryl, -OR₇, and -N(R₇)₂, and wherein R₇ is hydrogen or C₁-C₁₀ straight chained alkyl.

31. The compound of Claim 30, wherein R₇ is hydrogen or C₁-C₃ straight chained alkyl.

32. The compound of Claim 26, wherein R_2 is selected from the group consisting of hydrogen, hydroxy, nitro, aryl, heteroaryl, methoxy, and ethoxy.

33. The compound of Claim 26, wherein R_3 is selected from the group consisting of hydrogen, hydroxy, nitro, aryl, heteroaryl, amino, $-OR_7$, and $-N(R_7)_2$, and wherein R_7 is hydrogen or C_1 - C_{10} straight chained alkyl.

34. The compound of Claim 33, wherein R_7 is hydrogen or C_1 - C_3 straight chained alkyl.

35. The compound of Claim 26, wherein R_3 is selected from the group consisting of hydrogen, nitro, aryl, heteroaryl.

36. The compound of Claim 26, wherein R_4 is selected from the group consisting of hydrogen, C_1 - C_{10} straight chained alkyl, hydroxy, nitro, amino, halogen, $-OR_7$, and $-N(R_7)_2$, and wherein R_7 is C_1 - C_{10} straight chained or branched alkyl optionally substituted with an aryl or heteroaryl.

37. The compound of Claim 26, wherein R_4 is selected from the group consisting of hydrogen, C_1 - C_3 straight chained alkyl, hydroxy, nitro, amino, halogen, $-OR_7$, and $-N(R_7)_2$, and wherein R_7 is C_1 - C_3 straight chained alkyl optionally substituted with an aryl.

38. The compound of Claim 26, wherein R_4 is selected from the group consisting of hydrogen, methyl, ethyl, hydroxy, nitro, amino, chloro, fluoro, methoxy, ethoxy, methylamino, dimethylamino, diethylamino, and benzyloxy.

39. The compound of Claim 26, wherein R_5 is selected from the group consisting of hydrogen, C_1 - C_{10} straight chained alkyl, hydroxy, nitro, amino, halogen, perhaloalkyl, $-OR_7$, and $-N(R_7)_2$, and wherein R_7 is C_1 - C_{10} straight chained or branched alkyl optionally substituted with an aryl or heteroaryl.

40. The compound of Claim 26, wherein R_5 is selected from the group consisting of hydrogen, C_1 - C_3 straight chained alkyl, hydroxy, nitro, amino, halogen, perhaloalkyl, $-OR_7$, and $-N(R_7)_2$, and wherein R_7 is C_1 - C_3 straight chained alkyl.

41. The compound of Claim 26, wherein R_5 is selected from the group consisting of hydrogen, hydroxy, chloro, bromo, trifluoromethyl, and methoxy.

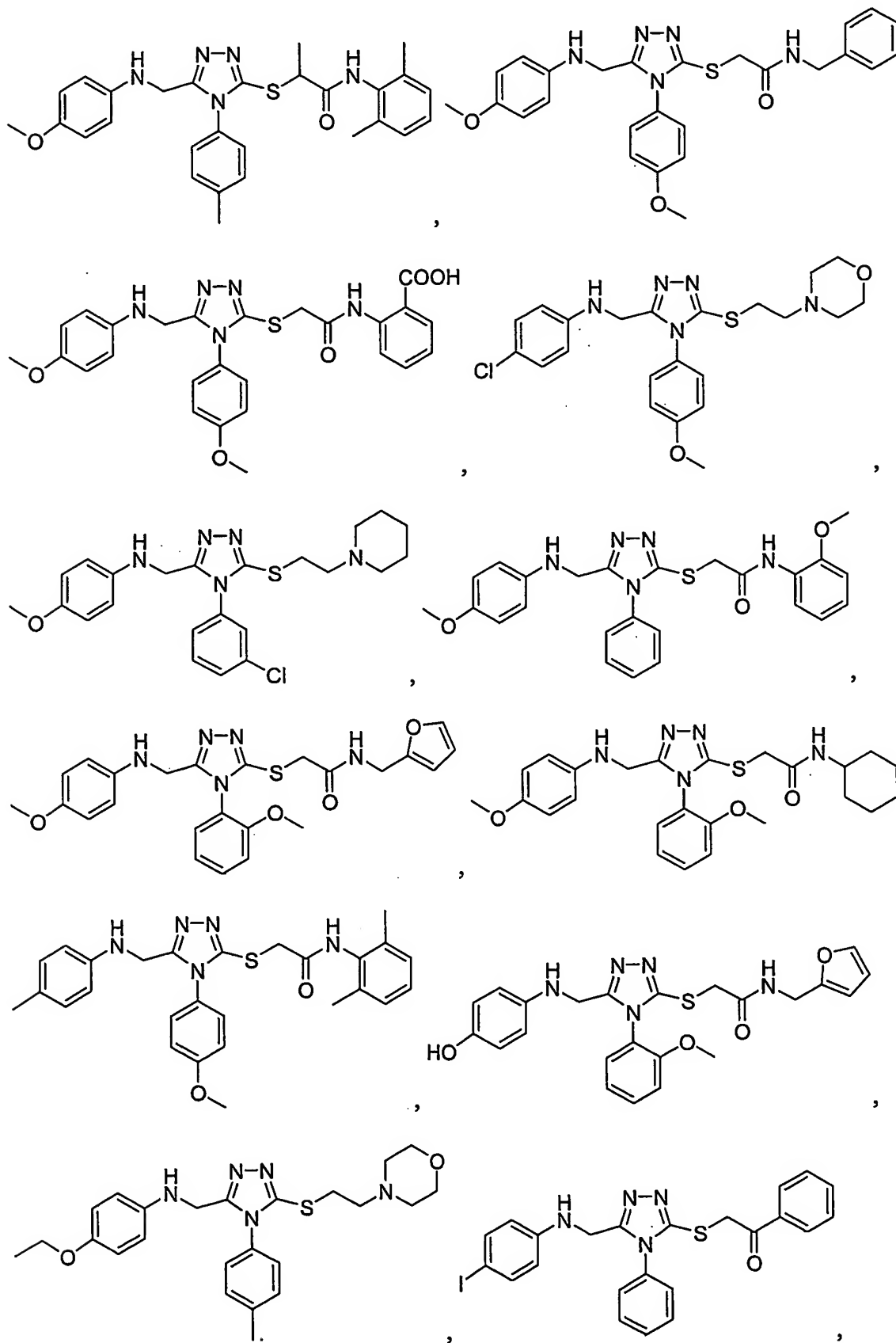
42. The compound of Claim 26, wherein R_6 is hydrogen.

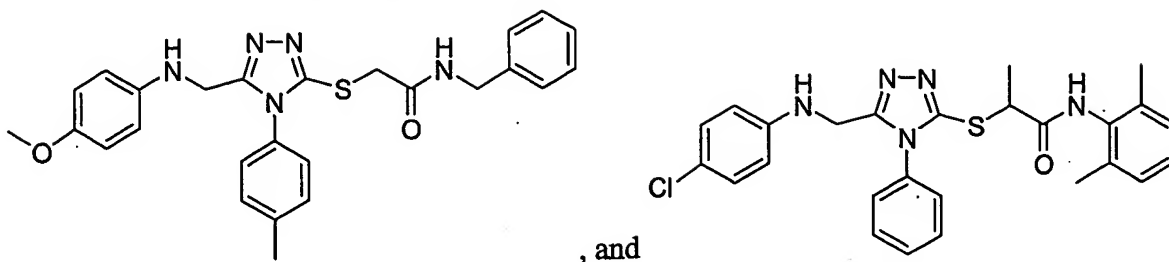
43. The compound of Claim 26, wherein R_2 and R_3 and the nitrogen to which they are attached form a fused heteroaryl or heterocyclic alkyl ring.

44. The compound of Claim 43, wherein the ring is a heterocyclic alkyl ring.

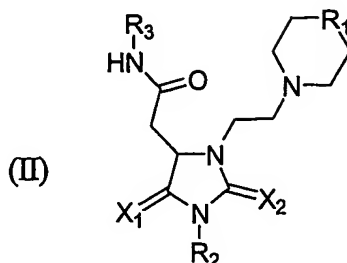
45. The compound of Claim 44, wherein the heterocyclic alkyl ring is selected from the group consisting of N-morpholine and pyrrole.

46. A compound selected from the group consisting of





47. A compound of Formula II



or a pharmaceutically acceptable salt, ester, amide, or prodrug thereof,

wherein

each of X_1 and X_2 is independently oxygen or sulfur;

R_1 is selected from the group consisting of C_1 - C_{10} straight chained or branched alkylene, oxygen, sulfur, NQ, CHCN, C=O, C=S, C=NQ, S=O, S(=O)₂, C=NOQ

wherein Q is selected from the group consisting of hydrogen, C_1 - C_{10} straight chained or branched alkyl optionally substituted with an aryl or heteroaryl, C_2 - C_{10} straight chained or branched alkenyl optionally substituted with an aryl or heteroaryl, C_2 - C_{10} straight chained or branched alkynyl optionally substituted with an aryl or heteroaryl, C_3 - C_{10} cycloalkyl, and C_5 - C_{10} cycloalkenyl;

each of R_2 , R_3 , is independently selected from the group consisting of hydrogen, C_1 - C_{10} straight chained or branched alkyl, C_2 - C_{10} straight chained or branched alkenyl, C_2 - C_{10} straight chained or branched alkynyl, C_3 - C_{10} cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, hydroxy, halogenated ether, nitro, amino, halogen, perhaloalkyl, $-OR_7$, $-N(R_7)_2$, $-CN$, $-C(=Z)R_7$, $-C(=Z)OR_7$, $-C(=Z)N(R_7)_2$, $-N(R_7)-C(=Z)R_7$, $-N(R_7)-C(=Z)N(R_7)_2$, $-OC(=Z)R_7$, and $-SR_7$,

wherein Z is oxygen or sulfur; and wherein each R₇ is independently selected from the group consisting of hydrogen, C₁-C₁₀ straight chained or branched alkyl optionally substituted with an aryl or heteroaryl, C₂-C₁₀ straight chained or branched alkenyl optionally substituted with an aryl or heteroaryl, C₂-C₁₀ straight chained or branched alkynyl optionally substituted with an aryl or heteroaryl, C₃-C₁₀ cycloalkyl, and C₅-C₁₀ cycloalkenyl.

48. The compound of Claim 47, wherein R₁ is selected from the group consisting of oxygen and NQ, wherein Q is selected from the group consisting of hydrogen, C₁-C₅ straight chained or branched alkyl optionally substituted with an aryl or heteroaryl.

49. The compound of Claim 48, wherein Q is C₁-C₃ straight chained or branched alkyl.

50. The compound of Claim 48, wherein Q is selected from the group consisting of methyl, ethyl, and propyl.

51. The compound of Claim 48, wherein Q is methyl.

52. The compound of Claim 47, wherein R₂ is selected from the group consisting of hydrogen, C₁-C₁₀ straight chained or branched alkyl, C₃-C₁₀ cycloalkyl, and optionally substituted aryl.

53. The compound of Claim 52, wherein R₂ is substituted aryl.

54. The compound of Claim 53, wherein R₂ is selected from the group consisting of 4-alkylphenyl, 4-alkoxyphenyl, 4-alkoxycarbonylphenyl.

55. The compound of Claim 53, wherein R₂ is selected from the group consisting of 4-methylphenyl, 4-ethoxyphenyl, and 4-ethoxycarbonylphenyl.

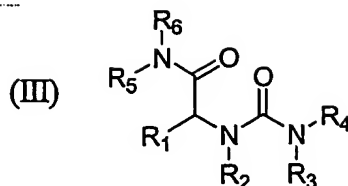
56. The compound of Claim 47, wherein R₃ is selected from the group consisting of hydrogen, C₁-C₁₀ straight chained or branched alkyl, C₃-C₁₀ cycloalkyl, and optionally substituted aryl.

57. The compound of Claim 56, wherein R₃ is substituted aryl.

58. The compound of Claim 57, wherein R₃ is selected from the group consisting of 4-alkylphenyl, 4-alkoxyphenyl, and 4-halophenyl.

59. The compound of Claim 58, wherein R₃ is selected from the group consisting of 4-chlorophenyl, 4-bromophenyl, and 4-methoxyphenyl.

60. A compound of Formula III



or a pharmaceutically acceptable salt, ester, amide, or prodrug thereof,

wherein

each of R_1 , R_2 , R_3 , R_4 , R_5 and R_6 is independently selected from the group consisting of hydrogen, C_1 - C_{10} straight chained or branched alkyl, C_2 - C_{10} straight chained or branched alkenyl, C_2 - C_{10} straight chained or branched alkynyl, C_3 - C_{10} cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic ring, hydroxy, halogenated ether, nitro, amino, halogen, perhaloalkyl, $-OR_7$, $-N(R_7)_2$, $-CN$, $-C(=Z)R_7$, $-C(=Z)OR_7$, $-C(=Z)N(R_7)_2$, $-N(R_7)-C(=Z)R_7$, $-N(R_7)-C(=Z)N(R_7)_2$, $-OC(=Z)R_7$, and $-SR_7$

wherein Z is oxygen or sulfur; and wherein each R_7 is independently selected from the group consisting of C_1 - C_{10} straight chained or branched alkyl optionally substituted with an aryl or heteroaryl, C_2 - C_{10} straight chained or branched alkenyl optionally substituted with an aryl or heteroaryl, C_2 - C_{10} straight chained or branched alkynyl optionally substituted with an aryl or heteroaryl, C_3 - C_{10} cycloalkyl, and C_5 - C_{10} cycloalkenyl; or

R_3 and R_4 and the nitrogen to which they are attached form a fused heteroaryl, or heterocyclic ring;

R_5 and R_6 and the nitrogen to which they are attached form a fused heteroaryl, or heterocyclic ring; or

R_1 , R_2 , the carbon to which R_1 is attached, and the nitrogen to which R_2 is attached form a fused heteroaryl, or heterocyclic ring.

61. The compound of Claim 60, wherein R_1 is selected from the group consisting of hydrogen and optionally substituted C_1 - C_{10} straight chained or branched alkyl.

62. The compound of Claim 61, wherein R_1 is C_1 - C_5 straight chained alkyl optionally substituted with an aryl or heteroaryl ring.

63. The compound of Claim 62, wherein said aryl ring is phenyl.
64. The compound of Claim 62, wherein said heteroaryl ring comprises nitrogen.
65. The compound of Claim 64, wherein said heteroaryl ring is indole.
66. The compound of Claim 61, wherein said R₁ is selected from the group consisting of methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, and tert-butyl.
67. The compound of Claim 60, wherein said R₁ is selected from the group consisting of methyl, indolylmethyl, benzyl, and sec-butyl.
68. The compound of Claim 60, wherein R₁, R₂, the carbon to which R₁ is attached, and the nitrogen to which R₂ is attached form a fused heteroaryl, or heterocyclic ring.
69. The compound of Claim 68, wherein said heterocyclic ring is pyrrolidine.
70. The compound of Claim 60, wherein R₂, R₃, and R₅ are each independently selected from the group consisting of hydrogen, C₁-C₄ straight chained or branched alkyl, C₂-C₅ straight chained or branched alkenyl, and C₂-C₅ straight chained or branched alkynyl.
71. The compound of Claim 70, wherein said alkyl is selected from the group consisting of methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, and tert-butyl.
72. The compound of Claim 60, wherein R₂, R₃, and R₅ are hydrogen.
73. The compound of Claim 60, wherein R₄ is optionally substituted aryl.
74. The compound of Claim 73, wherein said aryl is phenyl.
75. The compound of Claim 73, wherein said aryl is optionally substituted with halo, alkoxy, alkyl, alkylthio, and perhaloalkyl.
76. The compound of Claim 73, wherein said aryl is optionally substituted with chloro, bromo, methyl, ethyl, isopropyl, methoxy, methylthio, and trifluormethyl.
77. The compound of Claim 73, wherein R₄ is selected from the group consisting of 4-chlorophenyl, 4-bromophenyl, 4-methylphenyl, 4-ethylphenyl, 2,6-diisopropylphenyl, 3,4-dichlorophenyl, 4-methoxyphenyl, 4-methylmercaptophenyl, and 4-trifluoromethylphenyl.
78. The compound of Claim 60, wherein R₆ is selected from the group consisting of optionally substituted C₁-C₁₀ straight chained or branched alkyl, and optionally substituted heterocyclic ring.

79. The compound of Claim 78, wherein said alkyl is selected from the group consisting of methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, tert-butyl, pentyl, and 1-methylbutyl.

80. The compound of Claim 79, wherein said alkyl is substituted with a heterocyclic ring or a substituted amine.

81. The compound of Claim 80, wherein said heterocyclic ring is morpholine.

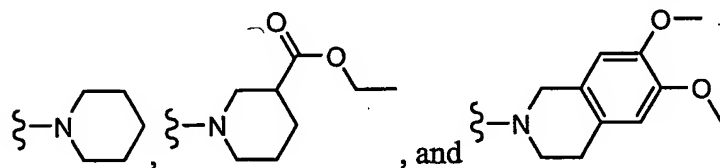
82. The compound of Claim 80, wherein said heterocyclic ring is piperidine or morpholine.

83. The compound of Claim 60, wherein R_6 is selected from the group consisting of 1-methyl-4-diethylaminobutyl, 2-N-morpholinoethyl, and N-benzylpiperidin-4-yl.

84. The compound of Claim 60, wherein R_5 and R_6 and the nitrogen to which they are attached form an optionally substituted fused heteroaryl, or an optionally substituted heterocyclic ring.

85. The compound of Claim 84, wherein said heterocyclic ring is piperidine or benzopiperidine.

86. The compound of Claim 60, wherein R_5 and R_6 and the nitrogen to which they are attached form a substituent selected from the group consisting of



87. A compound selected from the group consisting of

